REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-13 were presented for examination. Claims 9, 10, and 13 have been cancelled. Claims 7, 11, and 12 have been withdrawn from consideration.

Claims 14-31 have been added to the application. These claims are derived from claims 1-8. Specifically, claims 14-18 are similar to claims 1 and 3-8 in that all of these claims relate to treating "an acute or chronic spinal cord lesion." These claims differ from each other in the recitation of the compounds used in the treatment methods.

Claims 19-31 are also similar to claims 1 and 3-8, except that claims 19-31 are limited to treating "Alzheimer's disease." Claims 19-23, 24-27, and 28-31 differ from each other in the definition of the compounds used in the treatment methods.

Thus, claims 1, 3-6, 8, and 14-31 are presented for reconsideration.

Applicant acknowledges the courtesy extended to their representative during an interview on June 3, 2010. While agreement on patentability was not reached, Applicant gratefully acknowledges the Examiner's indication that the requirement for an election of species would be withdrawn. As is evident from the foregoing amendment of the claims, the claims now read on the treatment of an acute or chronic spinal cord lesion in a patient or the treatment of Alzheimer's disease in a patient. These indications were recited in claim 2.

Priority

Acknowledgment was made of Applicant's claim for foreign priority based on the application filed in France on January 17, 2003. The Examiner noted that Applicant did not file a certified copy of the English translation of the foreign application. Office Action at 2. Filed herewith is a verified English translation of French Application No. 03/00507, which perfects Applicant's priority claim under 35 U.S.C. § 119.

Background

A deterioration of neuronal cytoskeleton is observed in the majority of CNS lesions and neurodegenerative diseases. This deterioration can be the consequence but also the cause of damage to the affected cells. Indeed, microtubule depolymerization can be directly responsible for the dysfunction of certain neurons and can result in their death. Moreover, this deterioration affects the number and the length of the neuritic extensions of the remaining neuronal cells and, as a consequence, decreases their effectiveness. *See Specification at ¶ [0002].*

MAP2 proteins represent one of the major components of the proteins associated with neuronal microtubules. They are present in all the extensions which constitute the dendritic arborization of a neuron. MAP2 proteins are absolutely necessary for the formation of dendrites. *See Specification at ¶ [0004].*

The invention involves a novel use of neurosteroid derivatives to treat acute or chronic nervous system lesions, in particular, certain neurodegenerative diseases, linked to the ability of these derivatives to stabilize and/or increase the polymerization of neuronal microtubules. *See Specification at ¶ [0001].*

PREG is the precursor of all steroid hormones. Their synthesis implies the conversion of the PREG structure Δ5-3β-OH to Δ4-3-keto (implemented by an enzyme called 3βHSD). Applicant blocked the Δ5-3β-OH structure to prevent its metabolism and also to prevent the formation of the ester sulfate of PREG, a molecule that can be neurotoxic at high concentrations. The invention relates to 3-methoxy-PREG, and other molecules derived from pregnenolone that contain a 3-methoxy function or present a 3' function that can be converted into 3-methyl-ether. These molecules are incapable then of being converted into metabolites endowed with progestative (progesterone is a direct metabolite of PREG and, in addition to its hormonal activity, it is a PREG antagonist for the polymerization of microtubules), androgenic, estrogenic, and glucocorticoid activity. Also, they cannot be converted into ester sulfates which, like the sulfate of PREG, can have neurotoxic effects. *See Specification at ¶¶ [0009] - [0010].*

Preferred embodiments according to the invention, relate to the treatment of Alzheimer's disease and a lesion of the spinal cord, in particular medullary compression. Applicant demonstrated success in the treatment of animal models of these diseases. See Examples 5 and 7 in the Specification. The claims have been amended to read on the treatment of these diseases.

Claim Rejections - 35 USC § 112 - first paragraph

Scope of Enablement of the Invention

Claims 1-6, 8, and 13 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner stated that the claims contain subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Office Action at 3.

The Examiner found that claim 1 is enabled for treating an acute or chronic lesion using the compounds: 3β-methoxy-pregna-5-ene-20-one (3-methoxy-PREG), 3β-methoxy-pregna-5-ene-20-one-17α-dichloromethyl, and 3β–methoxy-5α-pregnone-20-one. Office Action at 6. Thus, claims 1-8 should be found to be enabled by the specification since these claims are directed to a method for treating an acute or chronic lesion using these compounds.

The Examiner also found that the specification discloses that the compound 3β-methoxy-pregna-5-ene-20-one (3-methoxy-PREG) is effective for treating Alzheimer's disease. Office Action at 4 and 6-7. Claims 19-23 should be found to be enabled by the specification, since these claims are directed to the treatment of Alzheimer's disease using 3-methoxy-PREG.

Having found that the specification is enabled for some indications using certain compounds, the Examiner's rejection for lack of enablement appears to be directed to the scope of the claims. Specifically, the Examiner stated that claim 1 is broader in scope than the enabling disclosure because the specification merely discloses that the compounds: 3β-methoxy-pregna-5,14-diene-20-one; 3β-methoxy-PREG-16α, 17α-epoxy and 3β-methoxy-PREG-16α, 17α-methylene, which are derived from PREG-16α, 17α-epoxy and PREG-16α, 17α- methylene, are effective to stimulate the polymerization of microtubules induced by MAP2 and to stimulate neuritic sprouting, but Applicant is claiming utilizing any of the claimed compounds to treat an acute or chronic

lesion. Office Action at 5. Applicant notes that the claims have been amended to recite methods of treating acute or chronic spinal cord lesion or Alzheimer disease.

Similarly, the Examiner stated that the specification provides some results and working embodiments with respect to the administration of the compound: 3β-methoxy-pregna-5-ene-20-one (3-methoxy-PREG) for treating medullary compression and Alzheimer's disease, as well as the stimulation of neuritic sprouting. However, there is no example for the administration of other claimed compounds, and there is no example for the treatment of other diseases, i.e. multiple sclerosis, pain or neuritic pain, as claimed in the instant invention. Office Action at 7-8. As will be evident from the claim amendments, the claims do not recite treatment of multiple sclerosis, pain, or neuritic pain.

The Examiner also stated that the specification was not enabling for treating Parkinson's disease, age-induced memory loss, memory loss induced by the taking of substances, a traumatic lesion, a cerebral lesion, pain, nerve degeneration, and multiple sclerosis. Office Action at 4, 6, 7, and 8. Once again, as will be evident from the foregoing amendments, the claims do not recite treatment of these indications.

As support for the contention that the specification is not enabling for the use of all of the compounds recited in claim 1 for the treatment of spinal cord lesion (Office Action at 2) and Alzheimer's disease (Office Action at 6), the Examiner stated that the stimulation of neuritic sprouting produced by the compounds: 3β-methoxy-pregna-5, 14-diene-20-one; 3β-methoxy-PREG-16α, 17α-epoxy and 3β-methoxy-PREG-16α, 17α-methylene (based on the results of PREG-16α, 17α-epoxy and PREG-16α, 17α-

methylene), was lower than that produced by pregnenolone (the control), citing the specification at page 21-22, Example 10. Office Action at 5. That is, only 3 compounds (3-methoxy-PREG, 3β-methoxy-pregna-5-ene-20-one-17α-dichloromethyl, and 3β-methoxy-5α- pregnane-20-one) were deemed to be enabled, because only those three compounds show higher activity *in vitro* than pregnenolone (PREG) in the Table of Example 10 in page 22. Office Action at 5.

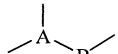
Applicant courteously disagrees with this analysis. Indeed, the application does not aim at providing compounds with higher *in vitro* activity on microtubules than PREG. It aims at providing compounds with higher activity on microtubules *in vivo* due to the presence of a 3-methoxy group in position 3 instead of a hydroxyl group.

The 3-methoxy group prevents metabolization of the compounds into compounds that do not have this activity (such as progesterone). While 3-methoxy-PREG is further advantageous because its *in vitro* activity is higher than PREG, it is not the only aim of the application.

The Table on page 22 (Example 10) shows that compounds other than PREG and 3-methoxy-PREG, some of which have a 3-methoxy group and others do not, are able *in vitro* (i.e. where there is no possibility of metabolization) to act on the polymerization of microtubules and on neurite growth. This Table also shows that the conversion of a 3-hydroxy (3-OH) group into a 3-methoxy group does not abolish this activity, since 3-methoxy-PREG activity is even higher than that of PREG.

Since the 3-methoxy group hampers metabolization *in vivo* into further metabolites that do not have activity on microtubule polymerization (such as

progesterone), the 3-methoxy compounds described in the Table on page 22 or the 3-methoxy compounds corresponding to the compounds described in this Table having a 3-OH group will necessarily have higher activity on microtubules *in vivo*, since they cannot be converted into inactive metabolites.

Enclosed is a Table summarizing the 

, R1, R2, and R3 substituents for all compounds described in the Table on page 22. As appears clearly from this Table, formula I corresponds to a very limited generalization of the substituents present in the compounds of the Table. Further, the Table on page 22 (Example 10) actually presents working criteria for the claimed methods. In particular, claim 1 is of reasonable scope in view of these teachings.

Applicant submits that the teachings in the specification, and the Table on page 22, are sufficient to enable the use of all 3-methoxy compounds claimed or described in the Table or corresponding to the compounds described in this Table having a 3-hydroxy group for the treatment of acute or chronic spinal cord lesion or Alzheimer's disease. There seems to be no dispute that a person of ordinary skill in the art would be able to make each of the compounds recited in the claims. Further, there seems to be no dispute that the teachings in the specification are sufficient to enable one to administer these compounds to a patient. Moreover, there seems to be no dispute that the specification clearly teaches that these compounds are useful for treating an acute or chronic spinal cord lesion in a patient or for treating Alzheimer's disease in a patient. A specification that discloses the manner and process of making and using an invention

in terms that correspond in scope to those used in defining the subject matter sought to be patented must be taken as in compliance with the enablement requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi,* 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Here, the specification expressly describes the compounds, enables their administration and use, and teaches that they are useful for treating the claimed indications. Thus, in the absence of reasons to doubt the objective truth of the statements contained in the specification, Applicant respectfully submits that the enablement requirements of §112 have been met and that the rejection should be withdrawn.

Claim Rejections - 35 USC § 112 - second paragraph

Claim 2 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. All dependent claims were included in this rejection. Office Action at 10.

Claim 2 was rejected because the claim was written using improper Markush format. Office Action at 11. In addition, claim 2 recited a broad limitation together with a narrow limitation that falls within the broad range or limitation (in the same claim). The claim was considered indefinite, since the resulting claim did not clearly set forth the metes and bounds of the patent protection desired. *Id.* Furthermore, claim 2 recited the term "notably" which renders the claim indefinite. *Id.*

This ground for rejection has been overcome by the amendment of claim 2 to recite "medullary compression" only. Thus, the rejection may be withdrawn.

Claim Rejection - 35 U.S.C. § 102

Claims 1-6, 8, and 13 were rejected under 35 U.S.C. § 102(a) as being anticipated by Baulieu et al. (EP 1 310 258). Office Action at 12.

The Examiner contends that Baulieu discloses a method for the enhancement of memory and cognitive functions by administering to an individual a therapeutically effective amount of an enantiomer of a steroid, wherein the individual has suffered memory loss resulting from a cause of age, i.e. normal, age related memory loss or dementia; neurological disorders, neuro-psychiatric disorders, i.e. anxiety, chronic stress, depression, sleep disturbance, drug related memory loss; neurodegenerative disorders, i.e. Alzheimer's disease; and amnesia resulting, i.e. from an injury or other trauma. Office Action at 13. The Examiner also contends that Baulieu discloses that the suitable steroid enantiomer, i.e. 3β-methoxy-pregna-5-ene-20-one or 3β-methoxy-pregnane-20-one, can be used. *Id.*

It appears that Baulieu was cited because Applicant's priority claim had not been perfected. Filed herewith is a verified English translation of the French priority application, which text is very close, although not identical, to the present application text.

Applicant submits that Baulieu is not prior art under 35 U.S.C. § 102(a). Baulieu was published on May 14, 2003, while Applicant's French priority application was filed on January 17, 2003. Thus, Applicant's effective filing date antedates the publication date of Baulieu.

Applicant draws the Examiner's attention to the fact that EP 1 310 258 is the priority application of PCT application WO 03/039554, which was filed in the English language on November 8, 2002, and published on May 15, 2003, but this PCT application does not seem to have entered U.S.

Claim Rejections - 35 U.S.C. § 103

Claims 1-6 and 8 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Chopp et al. (U.S. Patent No. 6,245,757). This ground for rejection is respectfully traversed.

The Examiner contends that Chopp teaches a method for the treatment of ischemic damage, i.e. damage due to stroke, comprising administering to a mammal afflicted with ischemic cell damage an effective amount of a pharmaceutical composition comprising progestin and a pharmaceutically acceptable delivery vehicle. The Examiner also contends that Chopp teaches that the method functions by the ability of the progestin or its derivative to reduce the damage caused by ischemia, i.e. brain damage caused by cerebral ischemia, and as a result, ischemic tissue, including tissue of the central nervous system or muscle tissue. Office Action at 14-15. Further, the Examiner contends that Chopp teaches that the progestin or its derivatives include progenenolone and pregnenolone methyl ether, and that the progestin or its derivatives

can be formulated as pharmaceutical formulations and administered to a mammal, i.e. human patient, in a variety of unit dosage forms. For oral administration, the progestin can combine with or more pharmaceutical excipients, so that the progestin is formulated to pass through the blood-brain barrier and enter the central nervous system at widespread sites and can effectively reduce infarct size following acute, focal ischemia, i.e. middle cerebral artery occlusion, when given before and after the onset of ischemia. Office Action at 16.

With respect to the recitation of the types of disease, i.e. an acute lesion, memory loss induced by a traumatic lesion, a cerebral lesion, ischemia, as claimed in claim 1 and claim 2, the Examiner stated that Chopp teaches that the treatment method utilizes the progestin or its derivatives for reducing ischemic damage due to stroke or myocardial infarction (see Abstract), wherein the treatable ischemia can result from brain damage caused by cerebral ischemia. The Examiner stated that the teachings of Chopp meet the recitation of "an acute lesion" in claim 1 and the recitation of "a traumatic lesion", "a cerebral lesion" and "ischemia", as claimed in claim 2. Office Action at 16-17.

The Examiner concluded that it would have been obvious to a person of ordinary skilled in the art at the time the invention was made to follow the guidance of Chopp to arrive at the instant invention. According to the Examiner, one of ordinary skill would have been motivated to try and choose progestin or its derivative, i.e. pregnenolone methyl ether, for reducing the brain damage caused by ischemia, for improving the neurological functions and for enhancing the ability of the brain to recognize after

damage and its intrinsic ability to compensate for injury because the prior art suggested for doing so. *Id.*

Chopp relates to a method for the treatment of ischemia, which is a lesion consecutive to a decrease or interruption of the blood supply (see Chopp, column 1, lines 9-10). The inventors of Chopp clearly indicate that they refer to ischemia due to stroke (a cerebrovascular disease, see Chopp, column 1, line 26) or infarct (see Chopp, column 2, line 29). Claims 1, 3-8, and 14-18 are now limited to the treatment of a spinal cord lesion, and claims 19-31 are limited to Alzheimer's disease. Chopp does not suggest that the compounds recited in Applicant's claims are useful for the treatment of spinal cord lesions or Alzheimer's disease.

Claims 1-6 and 8 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Stein et al. (U. S. Patent No. 2002/0072509). Office Action at 19. This ground for rejection is also respectfully traversed.

The Examiner stated that Stein teaches a method and a composition for the treatment of neuro-degeneration following a traumatic injury to the central nervous system by reducing or eliminating neuronal cell death, edema, ischemia, and enhancing tissue viability, such that the treatment can enhance survival, proliferation, or/and neurite outgrowth of the neurons that either prevent or retard neuro-degeneration, i.e. a progressive loss of neurons in the central nervous system. Office Action at 19-20. The Examiner also stated that Stein teaches that the neuro-protective method is achieved by the administration of a therapeutically effective composition comprising a progestin or a

progestin derivative to a patient, i.e. human, using progestin or its derivative, i.e. pregnenolone methyl ether. Office Action at 19-20.

With respect to the limitation where the composition is administered to the patient in an amount effective to stimulate polymerization and/or stabilization of microtubules in the patient, the Examiner noted that Stein teaches the steroid pregnenolone methyl ether, which is identical to the compound 3-methoxy-PREG as claimed. Since a chemical compound and its properties are inseparable, the Examiner concluded that, if the prior art discloses the identical chemical structure, the properties applicant discloses and/or claims are necessarily present, citing MPEP 2112.01: Part II and *In re Spada*, 911 F.2d 705, 709, 15 U.S.P.Q.2d 1655, 1658 (Fed. Cir. 1990).

The Examiner concluded that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to follow the guidance of Stein to arrive at the instant invention. According to the Examiner, one of ordinary skill would have been motivated to try and choose a progestin or its derivative, i.e. pregnenolone methyl ether, for reducing the brain damage caused by ischemia, for improving the neurological functions and for enhancing the ability of the brain to recognize after damage and its intrinsic ability to compensate for injury because the prior art suggested doing so. Office Action at 21-22.

Stein relates to a method for the treatment of CNS lesions, and more particularly, when looking at the description and even more at the working examples, to the treatment of a traumatic brain injury (TBI, see notably the Figure on the front page, numerous references to TBI in the description, and all experimental data). This

document does not suggest that the molecules recited in Applicant's claims be used for the treatment of an acute or chronic spinal cord lesion. In addition, one of ordinary skill in the art would not have reasonably expected that a compound shown to be useful for the treatment of TBI would also be useful for the treatment of spinal cord lesions. Indeed, the biological processes generated by a brain or spinal cord lesion are not identical.

For instance, the herein enclosed abstract by Schnell et al. clearly indicates:

> Trauma-induced lesions in brain and in spinal cord are associated with leukocyte infiltration, blood-brain barrier (BBB) breakdown, and secondary tissue destruction. Unexpectedly, these phenomena are generally more pronounced in the parenchyma of the spinal cord than in the parenchyma of the brain....Thus, using a minimally invasive injection technique, equivalent in both circumstances, we have shown that there are marked differences in the inflammatory response between the brain parenchyma and spinal cord parenchyma. This observation has important implications for the treatment of spinal cord injuries.

Thus, is appears that the secondary response due to trauma is more important in spinal cord lesions than in brain lesions.

Moreover, the herein enclosed Abstract by Widenfalk et al. further indicates that neurotrophic factors, which are important to stimulate neuronal survival and regeneration, show only limited upregulation in spinal cord after lesion. In particular, when stimulated with kainic acid, which is known to induce the expression of neurotrophic factors in brain, the response of spinal cord is much lower than brain response. ("The relatively limited upregulation of neurotrophic factors in the spinal cord contrasted with the response of affected nerve roots, in which marked increases of NGF

and GDNF mRNA levels were observed in Schwann cells. The difference between the ability of the PNS and CNS to provide trophic support correlates with their different abilities to regenerate. Kainic acid delivery led to only weak upregulations of BDNF and CNTF mRNA. Compared with several brain regions, the overall response of the spinal cord tissue to kainic acid was weak. The relative sparseness of upregulations for endogenous neurotrophic factors after injury strengthens the hypothesis that lack of regeneration in the spinal cord is attributable at least partly to lack of trophic support."). It thus appears that spinal cord is not able to express as much neurotrophic factors as brain after injury.

These two Abstracts clearly show that brain and spinal cord lesions cannot be considered as equivalent, and that regeneration of spinal cord may be difficult due to a more pronounced secondary response due to trauma and a lower expression of neurotrophic factors.

In addition, Stein does not suggest that the same compounds be used for the treatment of Alzheimer's disease. Alzheimer's disease is clearly distinct from traumatic brain injury, so that one of ordinary skill in the art would not have expected the compounds of Stein to be useful for the treatment of Alzheimer's disease.

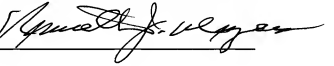
In summary, Applicant courteously submits that the claims are enabled by the specification and that the claimed subject matter is patentable over the prior art. Accordingly, allowance of the application at the Examiner's convenience is courteously solicited.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: September 1, 2010

By: 

Kenneth J. Meyers
Reg. No. 25,146
Phone: 202-408-4033
Fax: 202-408-4400
Email: ken.meyers@finnegan.com

Attachments: Verified English translation of French priority application
Table of Chemical Compounds
PubMed Abstract "Neurotrophic factors and receptors in the immature and adult spinal cord after mechanical injury or kainic acid.", Department of Neuroscience, Karolinska Institute, J. Widenfalk et al., and
PubMed Abstract "Cytokine-induced acute inflammation in the brain and spinal cord", CNS Inflammation Group, School of Biological Sciences, University of Southampton, L. Schnell et al.